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Alzheimer's Disease and the Neuroprotective Effects of Dietary Curcumin

Abstract

Alzheimer's disease is an irreversible and debilitating brain disorder that progressively decreases cognitive function. This disease is currently the 6th leading cause of death in the U.S. More recently, this ranking may have increased to the 3rd most common cause of death among persons over 60 years of age. Research has determined that a hallmark occurrence of Alzheimer's disease is the deposition of amyloid-beta protein plaques and tau proteins within the parenchyma of the brain. Given the disease's extreme effects on the brain and specifically on cognitive function, the FDA has approved medications that continue to provide improvement in cognitive function and ability. Researchers have recently discovered the efficacy of the herb curcumin (turmeric) whose effect is via its ability to destroy amyloid-beta plaques and increase cognitive ability in patients with Alzheimer's disease.

Keywords: Alzheimer's disease; Amyloid-beta plaques; Curcumin; Turmeric; Cognitive function

Review Article

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Brooks Nakia L[1], Meloche Theresa M[2], Brown Tony L[3]

[1]*University of Nebraska Medical Center, USA*
[2]*Major General Hugh G Robinson Center for Neuropsychiatry, USA*
[3]*Department of Neurology, Columbia College of Physicians and Surgeons, USA*

***Corresponding author:** Tony L Brown, Columbia University College of Physicians and Surgeons, USA, Tel: 267-973-615-6; Email: tbrown@post.harvard.edu

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Abbreviations: AB : Amyloid-Beta plaques ; AD: Alzheimer's Disease

Introduction

Alzheimer's disease (AD) and its associated dementia has a prevalence of over 3 million cases per year in the United States [1]. According to the National Institute of Health (NIH) and National Institute on Aging (NIA), AD is defined as an irreversible, progressive brain disorder that slowly destroys memory, thinking skills, and eventually the ability to perform the simplest of daily tasks [2]. Alzheimer's disease is currently the 6th leading cause of death in the U.S. More recently, this ranking has may have increased to the 3rd most common cause of death among persons over 60 years of age [1]. Alzheimer's is also the most common cause of dementia in older adults, and is known to lead to the loss of cognitive functioning that results in deficits of thought processes, memory, reasoning and simple behavioral abilities that allow humans to perform activities of daily living [1]. These tasks progressively become challenging and progressively are unable to be performed by those people who are afflicted with AD.

Pathophysiology of Alzheimer's Disease

Given that this disorder involves cognitive function deterioration, it is critical for scientists and medical professionals to establish a causal mechanism within the brain and nervous system. According to recent literature, damage to the brain precedes any obvious clinical signs or symptoms of the disease. The neuropathological process of AD consists of neuronal loss and atrophy, principally in the temporoparietal and frontal cortex [3]. During the pre -clinical stage, the main histological hallmarks observed in the brains of AD patients are senile plaques, neurofibrillary tangles and extensive neuronal loss. The mechanism of action of AD has been discovered to be dependent on the involvement of two proteins; amyloid-B-protein (AB protein) and tau protein, which are the main components of neurofibrillary tangles [4].

High levels of fibrillary AB protein are deposited in the brain of AD patients and manifest as loss of synapses and neurons along with impairment of neuronal functions. Further investigation has supported the theory that AB protein accumulation in the brain is the first pathological event leading to AD, given that genetic mutations and neurofibrillary tangles of the tau protein occur after the metabolism of the AB protein has been completed [5]. The AB protein deposited plaques have subsequently been the primary suspects and topics of discussion in regards to diagnostic criteria for AD, as well as the therapeutic targets.

Pharmacotherapies in Alzheimer's Disease

Over the years, the mainstay of therapy for AD has been pharmaceutical medications such as *donepezil (Aricept), revastigmine (Exelon), galantamine (Razadyne)* which are cholinesterase inhibitors, and *memantine (Namenda)*, which is an N -methyl-D- aspartate (NMDA) receptor antagonist. Cholinesterase inhibitors function by regulating neurotransmitters and improving the communication synapses that allow for stable cognitive function. A key neurotransmitter in this process is acetylcholine, which aids the maintenance of good communication connections between hippocampal cells and other neurons. As the level of acetylcholine (ACh) decreases, there are sporadic lapses of short-term memory leading to increased confusion. These medications are designed to decrease the breakdown of ACh, in an effort to improve the functionality of the hippocampal and neuronal cells. In comparison, *memantine* is a medication that protects brain cells by blocking the effects of excess glutamate. This medication is an *NMDA receptor antagonist*, whose action is reportedly to regulate the activity of glutamate, an important neurotransmitter

in the brain involved in learning and memory. Attachment of glutamate to cell surface docking sites of the NMDA receptors permits calcium to enter the cell. This process is important for cell signaling, as well as learning and memory. In Alzheimer's disease, excess glutamate can be released from damaged cells, which leads to chronic overexposure to calcium and which can speed up cell damage. *Memantine* helps prevent this destructive chain of events by partially blocking the NMDA receptors [6].

Again, these medications have been the mainstay of AD therapy for years. Although, there has been proven symptomatic benefit for many Alzheimer's patients after taking these medications, there are some detriments to these therapies, such as cost, potential side effects, availability, and the need for prescriptions. In addition to the desire to improve the quality of life for these patients, there is the necessity to develop (or locate) alternatives that are less costly, more abundant, less burdensome, more effective, and even preventive in the quest to conquer the multifactorial issues of AD. Is there an alternative form of therapy? The answer may not be further than the kitchen.

Herbal Therapy in Alzheimer's Disease

Curcumin (turmeric) is an ancient herb and spice that has been used in curry and other spicy dishes, and has been a culinary enjoyment of cultures around the globe. Over time, it has been noted that curcumin not only has culinary uses, but that is also has impressive medicinal qualities, particularly anti -inflammatory properties that have been shown to relieve pain and inflammation [3]. Originating from India, turmeric is a sterile, seedless plant that grows approx. 3 - 5 feet tall and has dull yellow flowers. The underground rhizomes (roots) of the plant have been used for medicinal and food preparation. The rhizome is boiled and dried to become turmeric [3]. The curcumin that is obtained from this plant was discovered to possess antiseptic, anti-inflammatory, and anti-cancer properties. Hence, it was used widely in areas of Asia and India as a medicinal agent. The incidence and prevalence rates of AD in India were observed to have been far lower than the rates in other countries, and consequently, researchers began to investigate the association between curry consumption and cognitive levels in Asia [7]. In one study, 1010 Asians cognitive abilities were compared to those of subjects who consumed curcumin vs. those who did not. The researchers reported that those participants who had occasionally or often eaten curry tended to perform better on standard cognitive testing, such as the Mini -Mental Status Exam, than those participants who had no curry consumption. Also noted was that patients who had consumed curcumin were able to perform activities of daily living (ADLs) with minimal or no difficulty. The studied ADLs included brushing teeth, buttoning shirts, setting alarm clocks, and recalling names and phone numbers [7]. Further research discovered that curcumin consumption not only improved AD from a symptomatic perspective, but also displayed encouraging effects at the molecular and cellular levels.

Mechanism of action of curcumin

As discussed previously, the deposition of AB plaques have been the hallmark sign of AD and the therapeutic target of pharmacologic treatments. The effects of curcumin on the prevention, reduction, or elimination of AB plaques, therefore, has a crucial role in the research goal to gain further insight into the amazing treatment properties of this spice. An interesting study of mice who were injected with AB plaques was conducted to identify whether or not there was a decrease in the levels of AB plaques in the mice that were fed curcumin. The study concluded that the levels of beta- amyloid had decreased by 40% in the mice that had received the curcumin compared to the mice that did not. In addition, the mice that received low doses of curcumin were found to have had a 43% decrease in the plaque deposits that had been artificially placed in their brains [8]. At the molecular level, curcumin at higher concentrations was found to bind to amyloid beta to block self -assembly. Due to the lipophilic nature of curcumin, it is able to cross the blood- brain barrier and bind to the plaques [9]. From this study, it was also noted that curcumin was a better A -beta 40 aggregation inhibitor and that the herb is a destabilizer of the A-beta polymer. In turn, this denatured the structural compound of the amyloid beta plaques and improved participants' overall cognitive function while resulting in a decreased rate of disease progression [9]. Curcumin was also noted have AD phagocytic mechanisms. Turmeric was found to restore the inhibitory effect of prostaglandin -E2 (PGE 2) on phagocytosis of AB proteins (specifically AB42) stimulated the N9 microglial cells. In AD patients, there is a significant decrease of AB42 activated microglial phagocytosis by exogenous PGE2 [10]. Impaired phagocytosis and increased expression of PGE2 occurs in the brains of AD patients, which suggested that there was failure of a clearing mechanism to remove inflammatory debris and neuronal 9 cells (N9 cells) that are tagged with AB proteins. N9 cells were pretreated with or without curcumin for 30 minutes prior to fibrillar AB peptide treatment. Statistical significance demonstrated that curcumin improved the phagocytic abilities by inhibiting the PGE2 system, which then allowed an increased activation of the inflammatory response that resulted in the clearance of AB plaques [11]. The study result revealed compelling evidence that demonstrated curcumin's significant effect on the breakdown and engulfing mechanisms ability to remove the beta-amyloid plaques in Alzheimer's disease (Figures 1 & 2).

Curcumin's Macrophage Activity

Studies have demonstrated that curcumin may help macrophages to clear amyloid plaques as well. A study conducted at UCLA had 9 subjects, 6 patients of whom had already been diagnosed with AD and 3 of whom did not have the disease. Beta -amyloid was then introduced into participant blood samples that were treated with curcumin. The patients with AD, whose macrophages and blood samples were treated with curcumin, showed an improved uptake and ingestion of the plaques. This finding is supportive of the prior research results, which indicated that curcumin is assistive to the immune system in its function of amyloid protein clearance [3]. Curcumin has also been shown to provide anti -inflammatory protection for nerve cells. This is important, given that another crucial aspect in regards to the pathogenesis of AD is the chronic inflammation of the nerve cells. Several studies have demonstrated that associated inflammatory changes, such as microgliosis and astrocytosis, as well as the

presence of pro - inflammatory substances that accompany the amyloid- beta plaque deposits. The implications of the turmeric/curcumin research revealed an encouraging sign of curcumin's ability to treat patients with Alzheimer's disease, and prevent the disease altogether. Aside from aforementioned benefits of this widely available herb, other properties include anti-oxidant and cholesterol-lowering capabilities [3]. Of further, and significant benefit, is that this root is less costly, has fewer (if any) side effects, and no prescription is needed in order to obtain it.

Chronic use of excessive amounts of curcumin has the potential to cause liver toxicity. For this reason, use in patients with liver disease is not recommended; this includes patients with biliary colic, cholecystitis, and jaundice. Curcumin also interacts with anticoagulants and some NSAIDS. Close monitoring of patients who are ingesting a combination of curcumin/turmeric and any medication with anticoagulant or hepatotoxicity properties should be performed [11].

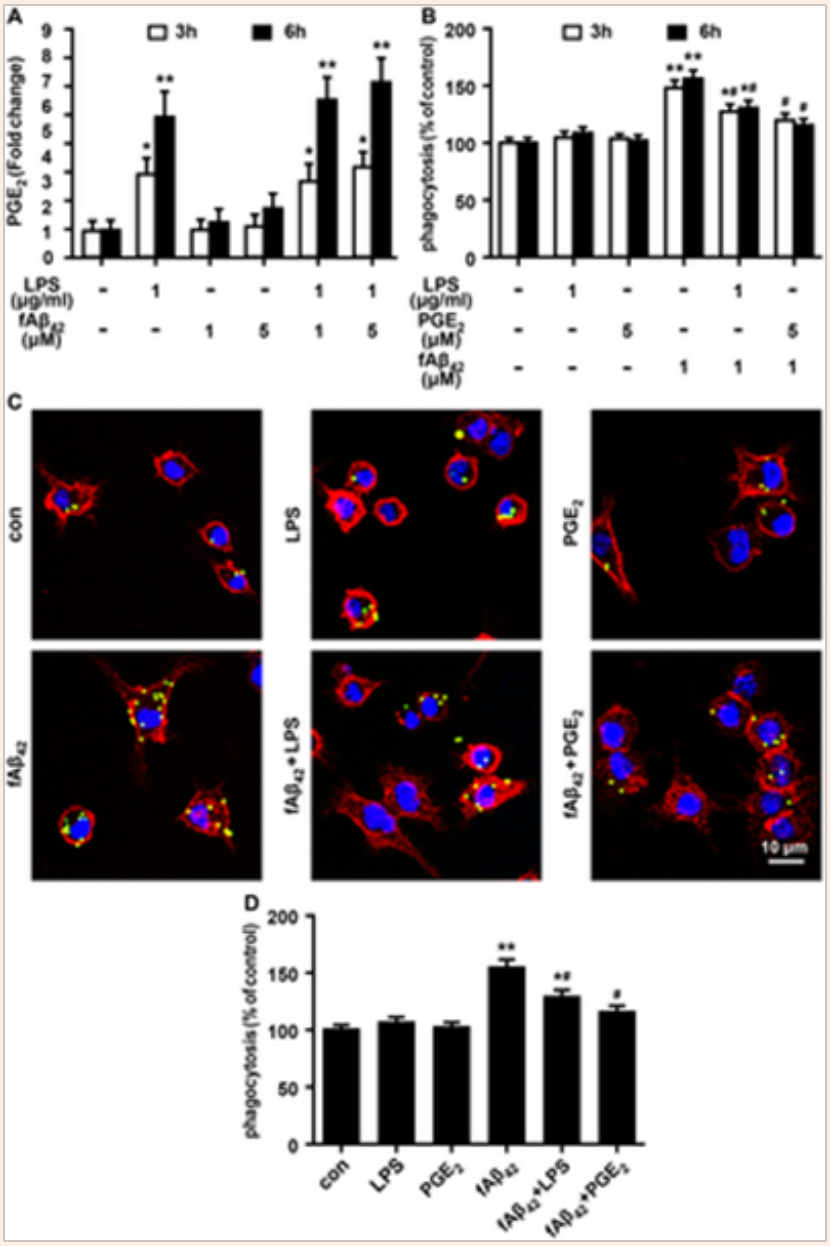

Figure 1: Effect of LPS and PGE_2 on $fA\beta_{42}$-induced phagocytosis in N9 cells.

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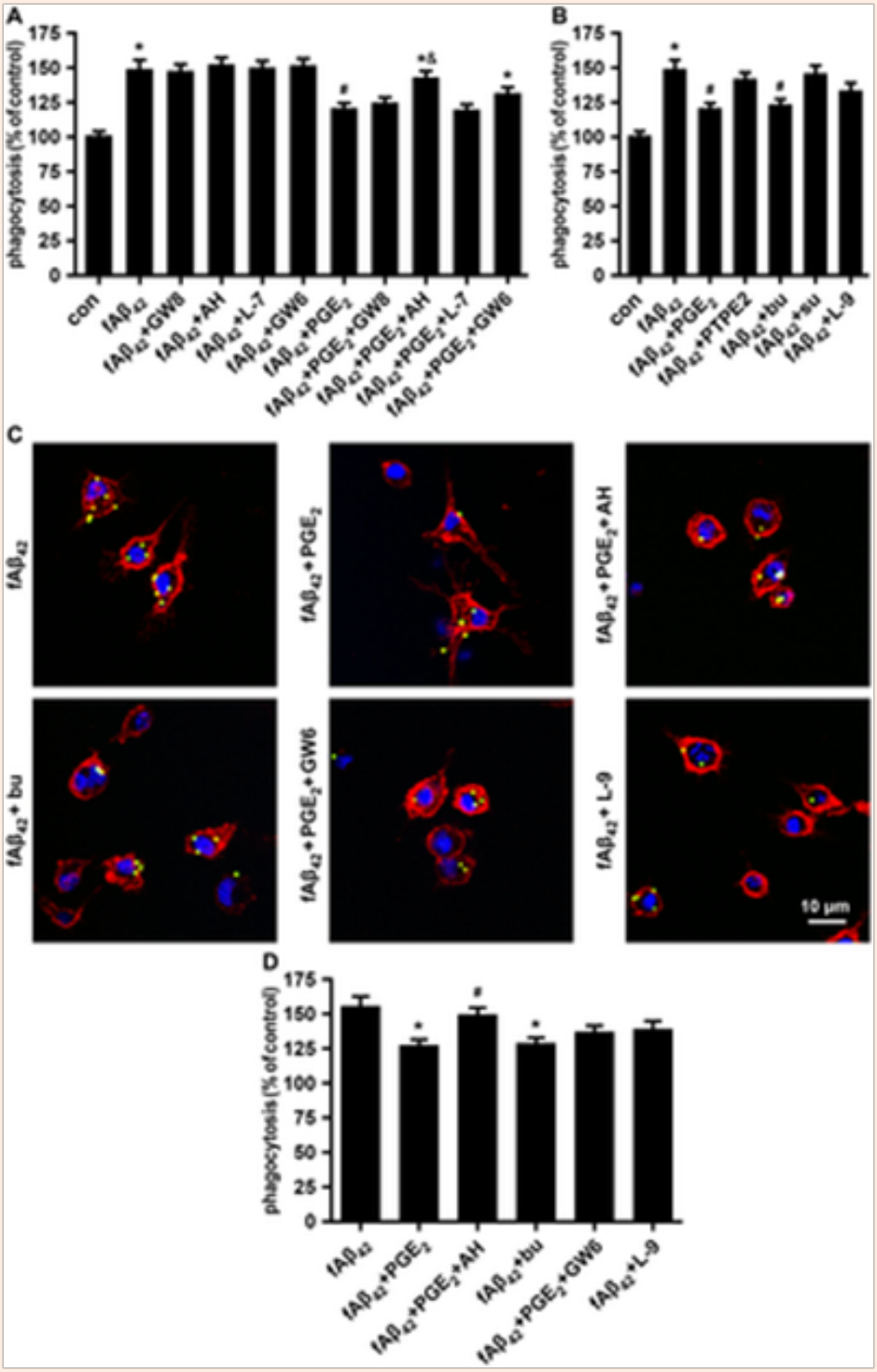

Figure 2: Effect of E-prostanoid receptors on fAβ_{42}-induced phagocytosis with or without PGE_2 in N9 cells.

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Conclusion

Curcumin appears to be a promising resource for the management and prevention of Alzheimer's disease. Studies have demonstrated that the administration of curcumin, in the pure form or as an adjunct chemical to current treatment compounds, can provide an inexpensive and widely available method for the improvement in the quality of life of those patients who are afflicted with the cognitive impairments of AD, and potentially, for other society members, as well. Already determined was that AD can be prevented through lifestyle modifications [12], which should be a primary focus of all research. Given the positive treatment response of those AD patients who were treated with curcumin, it appears that the benefits of using curcumin clearly outweigh the risks of not using it. Furthermore, it may be instructive to consider the increasing number of other herbal treatments that are available, such as coconut oil, the Indian herbs ashwagandha and bacopa monniera, and a phytophenol, resveratrol, which is present in red grapes [13].

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